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Unrecognized Errors Due to Analog Filtering of the Brain-Stem Auditory Evoked Response

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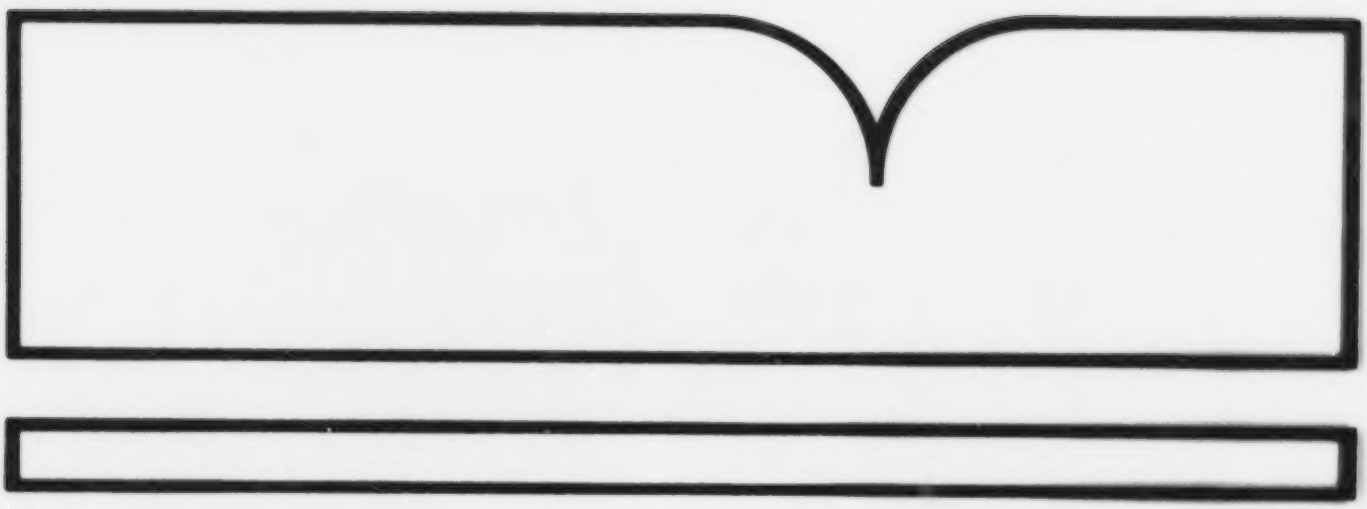

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16. ABSTRACT

The brainstem auditory evoked response (BAER) is used as a tool both in clinical evaluation (see Eggermont, 1983, and Sohmer, 1983, for summaries) and in toxicological research, where the subject is most often the laboratory rat (e.g. Amochaev, et al., 1979; Rebert, et al., 1983). As in other species, interpretation of the rat BAER waveform is based on the latencies and amplitudes of its voltage peaks, and the association of these peaks with ascending levels or nuclei of the auditory system (Jewett and Romano, 1972; Buchwald and Huang, 1975).

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UNRECOGNIZED ERRORS DUE TO ANALOG FILTERING OF THE BRAIN-STEM AUDITORY EVOKED RESPONSE

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Summary Analog filtering of the brain-stem auditory evoked response (BAER) and synthetic wave forms using steeply sloped filters are shown to produce significant distortion even when filter cut-off frequencies are well removed from the wave form spectrum. The degree of distortion is such that it may result in erroneous identification of peaks in the BAER. Reversal of the order of peaks may occur with high pass settings at only 1/4 the lowest constituent frequency.

Filter effects were identified as a major source of cross-laboratory differences in BAERs recorded from laboratory rats. Filter transfer functions of a typical analog filter set were derived for both gain and phase as a function of frequency. Filtering of synthetic wave forms was used to elucidate and highlight distortion effects. A typical Long-Evans rat BAER wave form was spectrum analyzed and conclusions were drawn with respect to appropriate bandpass frequencies.

Keywords: *analog filter – brain-stem auditory evoked response (BAER) – ABR – phase distortion – rat*

It is well known that analog filters produce phase distortion of time-varying signals in general (e.g., Dawson and Doddington 1973; Desmedt et al. 1984) and the brain-stem auditory evoked response (BAER) in particular (Boston and Ainslie 1980; Doyle and Hyde 1981; Elton et al. 1984). Implicit in the selection of filter cut-off frequencies by many investigators, and in the advice given in papers on the subject (e.g., Kevanishvili and Aphonchenko 1979; Osterhammel 1981; Doyle and Hyde 1981), is the assumption that setting bandpass limits on either side of the wave form spectrum will preclude distortion effects. For example, Kevanishvili and Aphonchenko (1979), who reported energy in the human BAER spectrum as occurring between 50 and 1000 c/sec, state that filters which attenuate frequencies below 80 and above 1000 c/sec should not produce 'any significant amplitude distortion of the recorded signal' (p. 55). Doyle and Hyde (1981), who showed differential percentages of phase and amplitude error across cut-off frequencies and roll-off slopes, investigated high pass cut-off frequencies within the reported power density spectrum. With respect to low pass filtering, they 'support the use of 2 kHz low pass filtering' (p. 88), which frequency they found to be the upper spectral limit.

The validity of this assumption is placed in question by the work of Elton et al. (1984) who showed that increasing the slope of the high pass filter affects the human BAER wave form in ways which are similar to those produced by increasing high pass cut-off frequency. While the demonstration by Elton et al. was done at a high pass setting within the spectrum of the BAER (150 c/sec; Elberling 1979; Kevanishvili and Aphonchenko 1979; Møller et al. 1981; Osterhammel 1981; Hoke et al. 1984), it is possible that similar effects may occur outside the reported spectrum. Although not documented by any reports, it seems likely that complementary distortion may occur with low pass filtering of BAERs.

These considerations have practical implications. For example, published rat BAERs are suf-

[1] This paper has been reviewed by the Health Effects Research Laboratory, U.S. Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use. Also to whom correspondence should be addressed.

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ficiently different from each other in latency, amplitude and general morphology (including the number of peaks present) that comparisons are difficult, even within the species. Since these wave forms are being used as the basis for extrapolating neurotoxic effects of environmental chemicals from rats to humans (e.g., Amochaev et al. 1979; Janssen et al. 1983; Rebert et al. 1983), avoidance of distortion of BAERs compared within and between species is critical to valid interpretation and extrapolation. That the differences between reported rat BAER wave forms may reflect varying degrees of filter-induced distortion is suggested by the observation that cut-off frequencies for recording rat BAERs range from 0.1 Hz to 400 Hz for high pass, and from 3 kHz to 10 kHz for low pass (Amochaev et al. 1979; Plantz et al. 1981; Rebert et al. 1982).

The following 3 experiments were conducted in order to quantify filter-induced distortion in the BAER using a wider range of bandpasses, to explore explicitly the relationships between filter gain and phase transfer functions, and to learn the degree of similarity between the rat BAER spectrum and the human BAER spectrum.

Experiment 1

Method and Material

Adult male Long-Evans hooded rats (N = 11) were implanted with 00-90x 1/16" stainless steel skull screw electrodes threaded into the skull at these locations: ground, 2 mm anterior to bregma and 2 mm to the right of midline; reference, 8 mm anterior to bregma on the midline; BAER active electrode, 2 mm posterior to lambda on the midline. Screw electrodes were connected to an Amphenol receptacle by nichrome wires, and the assembly was encased in dental acrylic. Surgeries were accomplished using non-rupture stereotaxic earbars. Nitrofurazone was applied to the wound margins and the animal was injected intramuscularly with penicillin G (100,000 units). Anesthetic used for surgery was Chloropent administered intraperitoneally (0.35 ml/100 g body weight).

Approximately 1 week after surgery, animals were tested individually as follows. The unanesthetized rat was placed in an open-topped chamber designed for acquisition of flash-evoked potentials (Dyer and Annau 1977). The rats were free to move within the 20 cm × 7.5 cm floor space of the chamber. The floor consisted of plexiglass bars about 2.5 cm apart, which produced no significant reflections of the auditory stimulus. This open box sat within a larger (73 cm × 61 cm × 73 cm) insulated chamber with a transmission loss (outside to inside) of at least 35 dB in the rats' range of auditory sensitivity (Kelly and Masterton 1977). A Motorola piezoelectric tweeter was mounted in the ceiling of this chamber 46 cm above the level of the animal's ears. Acoustic travel time from speaker to ears was about 1.4 msec.

Click stimuli, rarefaction square waves of 50 μsec duration, were generated by a stimulator and presented at a stimulation rate of 10/sec. An impulse level meter with a 0.5 in. microphone was used to measure stimulus levels. Peak sound pressure levels of the stimulus at the animal's ears was 90 dB, with no greater than 0.5 dB reflection at the chamber walls.

EEG was amplified (×10,000). Filtering of the EEG (before averaging) was accomplished by a variable analog filter [2] with a 48 dB/octave rolloff. Responses to 512 stimuli were averaged by a signal averager, using an epoch of 12 msec and a sampling interval of 3 μsec/point. The resulting wave forms were plotted by an X-Y plotter. Peak latencies and amplitudes were obtained via cursor controls.

Nine pairs of BAERs were collected consecutively from each rat in one session, in a two-way repeated measures design. Each pair of BAER wave forms consisted of an unfiltered (0.1 Hz–30 kHz bandpass, established by the limits of the amplifier) and a variably filtered wave form from the same set of 512 responses, in the sequence outlined in Table I. In runs 1 through 5, where high pass cut-off frequency was varied, the low pass cutoff of 30 kHz was imposed only by the amplifier. In runs 6 through 9, where low pass cutoff was varied, the high pass frequency was

[2] The commercial names of all the equipment used can be obtained from the authors.

TABLE I

Sequential order of filter cutoffs across runs.

Run no.	Unfiltered channel		Filtered channel	
	High pass (Hz)	Low pass (Hz)	High pass (Hz)	Low pass (Hz)
1	0.1	30000	3	30000
2	0.1	30000	30	30000
3	0.1	30000	100	30000
4	0.1	30000	200	30000
5	0.1	30000	300	30000
6	0.1	30000	0.1	1000
7	0.1	30000	0.1	3000
8	0.1	30000	0.1	10000
9	0.1	30000	0.1	30000

imposed by the amplifier. Thus, the filter was used only in establishing the cut-off frequencies being systematically varied. Run 9, then, provides a comparison of the effects of the 30 kHz filtering by the amplifier with those of the amplifier and the filter in combination on the same wave form. Wave forms were plotted in unfiltered-filtered pairs.

Each measure of latency and amplitude was analyzed using a two-way repeated measures

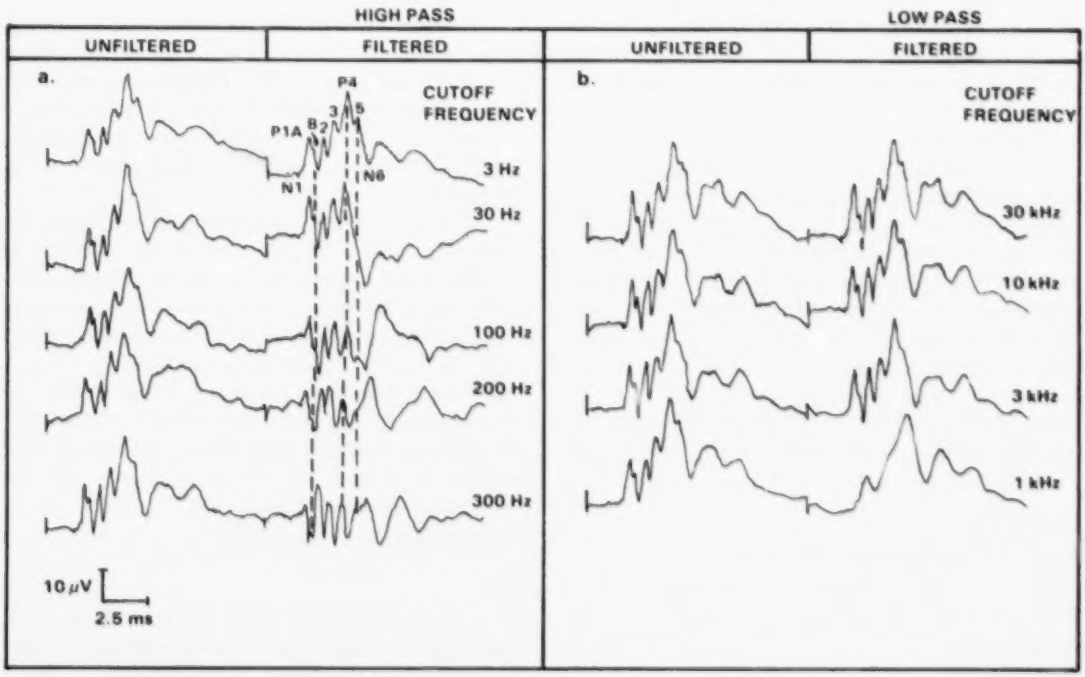

Fig. 1. Representative wave forms recorded from one animal. a: filtered and unfiltered wave forms from the high pass filter runs. b: filtered and unfiltered wave forms from the low pass filter runs.

ANOVA with channel (filtered vs. unfiltered wave form) and run (1 per filter setting) as repeated measures. Statistically significant channel by run interactions were submitted to simple effects analyses. An overall alpha of 0.05 was maintained by use of Bonferroni corrections.

Results

Sample wave forms from an individual rat are shown in Fig. 1. General effects of high pass and low pass filtering on both latencies and wave form morphology can be seen clearly. With progressively greater high pass filtering, latencies appear to decrease and the wave form gains a flatter appearance with a more regular oscillatory pattern. In addition, small peaks, especially P1B and P5, shift to positions of seemingly greater prominence. With progressively greater low pass filtering, latencies increase and, while overall amplitude seems not to change, peak-to-peak amplitudes seem to diminish somewhat.

A striking effect of low pass filtering at 1000 Hz was the disappearance or merging of peaks, as exemplified in Fig. 1. Table II shows the number of missing peaks for all animals by channels and runs.

The significance tests showed that peak latencies were decreased by high pass filtering. Statistical significance was reached as early as run 2 (30 Hz) for P4, and as late as run 4 (200 Hz) for P2. P1B and P5 were exceptional in that their latencies did not change. Peak-to-peak (i.e., preceding negative to positive peak) amplitudes were also affected by the high pass filter, with some amplitudes increasing and some decreasing with the treatment. Those which decreased with treatment were N1P1A, N1P1B, N3P3 and N4P4. The amplitudes N2P2 and N5P5 increased as high pass cut-off increased. The P4N6 amplitude, used as a measure of overall wave form size, was found to diminish with progressive high pass filtering. Fig. 2a–d show the effects of high pass filtering on selected measures: P1A and P4 latencies, and N5P5 and P4N6 amplitudes.

TABLE II

Numbers of missing peaks in low pass runs.

	Channel 1 unfiltered	Channel 2 filtered
Run 6 (1 kHz)	3	37
Run 7 (3 kHz)	3	3
Run 8 (10 kHz)	2	2
Run 9 (30 kHz)	3	3

Progressively greater low pass filtering increased mean latencies. The latencies of P1A and P4, which were present at all cut-off frequencies, are shown in Fig. 2e and f. The wave form was smoothed even at 10 kHz. In the 30 kHz low pass condition, which compared the effects of the variable filter with those of the amplifier, P1A latency was significantly, but only slightly, delayed by the variable filter and amplifier with respect to the amplifier filter alone. The low pass filter had no consistent effect on peak amplitudes.

Experiment II

Method and Material

In order to elucidate the temporal distortion due to high and low pass filtering, the frequency response and phase shift characteristics were empirically determined for the variable filter, using a signal generator and an oscilloscope. An algebraic expression for time shift through a filter was developed.

A single, sample input frequency, 2 Hz, and a high pass cut-off frequency of 0.5 Hz (3 dB down) were selected to illustrate the phase lead phenomenon in detail. Then, a slightly more complex wave was generated by use of a numerical series which was digital-to-analog converted by a microprocessor. This wave contained a slow oscillatory component (2 Hz) and a single fast transient. This wave form was then filtered by a high pass filter, again set at a 3 dB frequency of 0.5 Hz. All illustrative wave forms were plotted on a Hewlett-Packard X-Y plotter.

Results

Fig. 3a depicts the phase and gain response of the high pass filter for continuous sinusoids of any frequency. In the figure, 'f' denotes the nominal cut-off frequency as determined by the filter setting, and input frequencies are represented as

proportions of f. Note that, for all frequencies, the phase shift of the output with respect to the input is negative. Note also that the phase shift is quite extreme, even in frequencies which are relatively unattenuated. At the 3 dB point (0.71 on the gain function), for example, the phase shift due to high

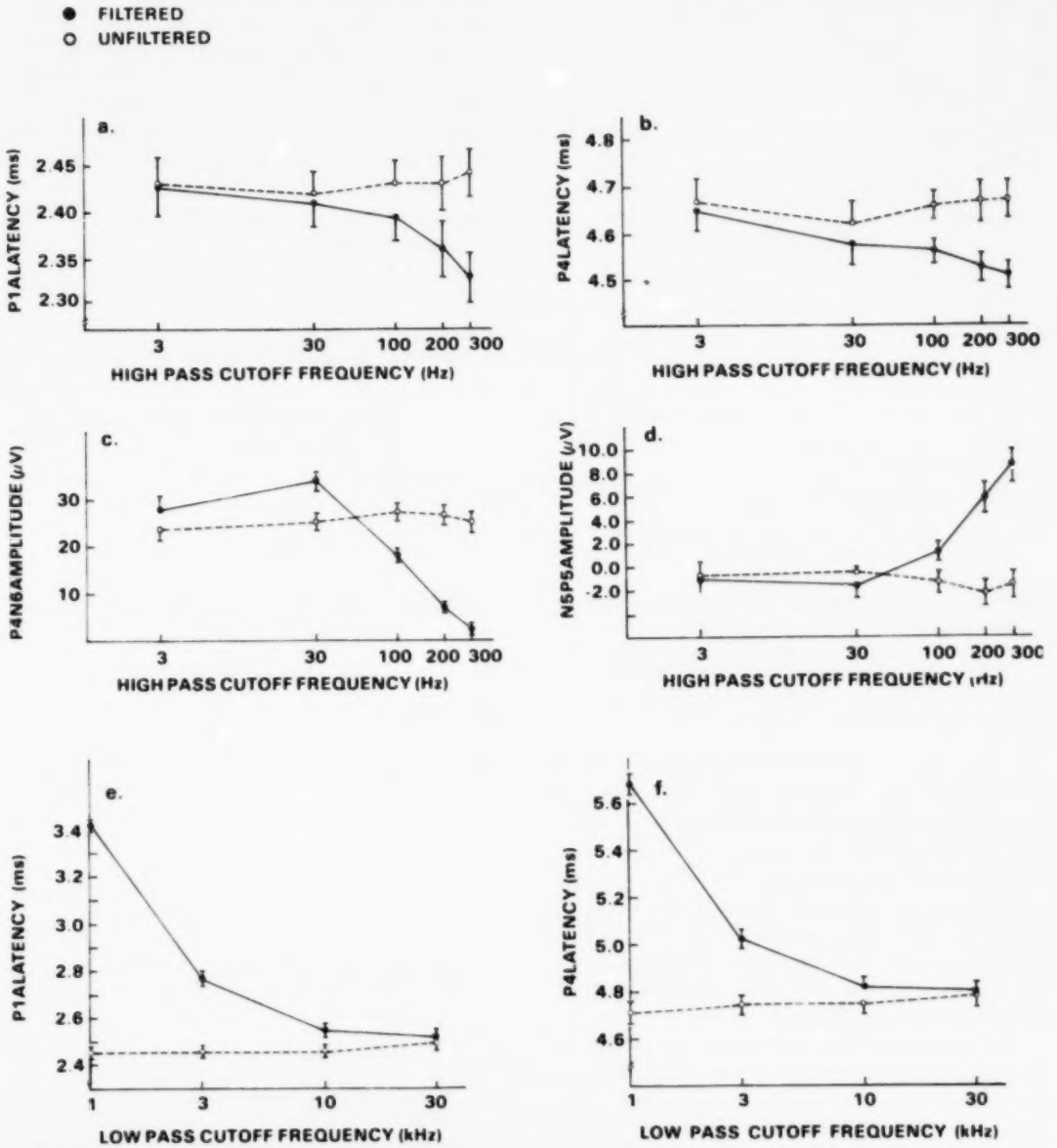

Fig. 2. Effects of filtering on selected wave form parameters. a: high pass effect on P1A latency. b: high pass effect on P4 latency. c: high pass effect on P4N6 amplitude. d: high pass effect on N5P5 amplitude. e: low pass effect on P1A latency. f: low pass effect on P4 latency. Open circles are means ± S.E.M. from unfiltered wave forms. Filled circles are means ± S.E.M. from filtered wave forms.

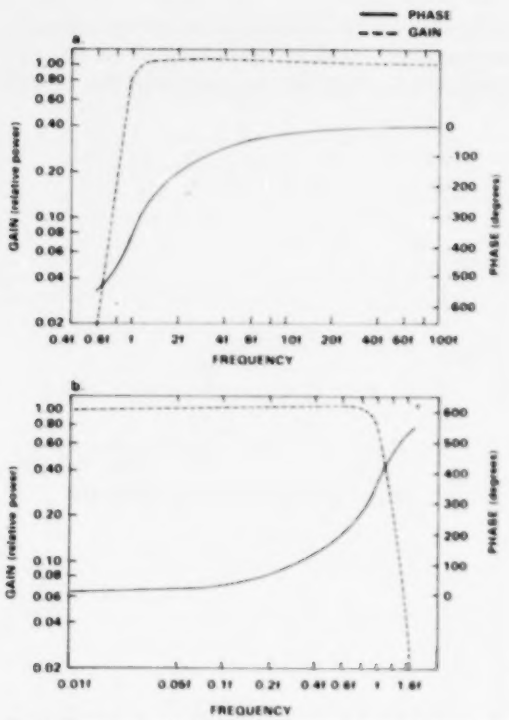

Fig. 3. Phase and gain functions, showing effects of filtering at nominal cut-off frequency, f, on wave form component frequencies, which are shown as multiples of f. a: high pass filter transfer functions. b: low pass filter transfer functions.

pass filtering is $-360°$. Even for frequencies which are relatively unattenuated, phase distortion can be great; a signal component frequency 10 times the cut-off frequency will be phase shifted $-30°$. Similar effects are seen in Fig. 3b, where low pass relationships are depicted. The direction of phase shift is positive here. At 3 dB down, the shift is 360°. Phase shift due to low pass filtering mirrors that due to high pass: a 30° shift occurs in a signal frequency which is 10% of the cutoff.

The observed phase shifts may be expressed mathematically in terms of relative time. Proportional time shift of a continuous sinusoid is expressed by $\Phi/360°$, where Φ is the phase shift in degrees. The time required for the wave to complete one cycle is $1/f$, where f is equal to the sinusoid frequency. Thus the time by which the output wave appears to lead or lag the input to a filter is $\Phi/360$ f.

Fig. 4a shows a case in which the input to the high pass filter was 3 cycles of a 2 Hz sinusoid. During the first full cycle of the filtered output, the wave is gradually increasing in amplitude. This represents a period of time during which the filter's reactive components are being charged. In fact, stable output is reached as an exponential function of time over several time constants, depending on the design of the particular filter. After the input wave ends, the output continues for a period of time determined by the time constant. The simple expression above for time lead or lag only holds for a continuous sinusoid, a poor model of physiological signals.

In order to further explore the problems of

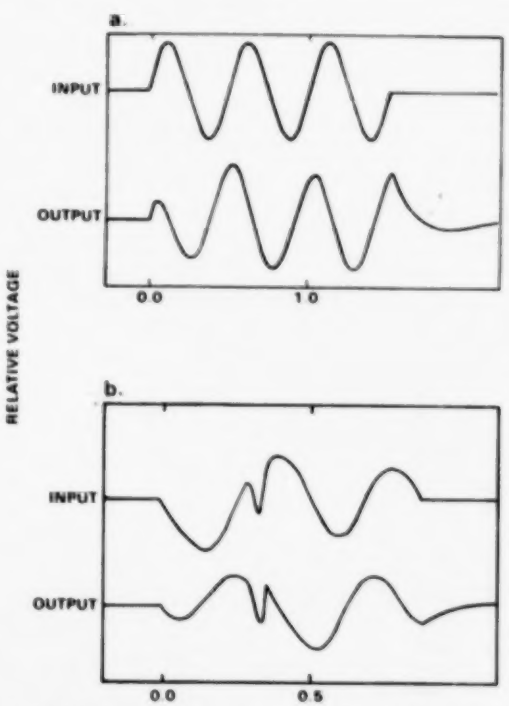

Fig. 4. High pass filter effects on synthesized wave forms. a: input function is 2 Hz sinusoid; output has been high pass filtered using 0.5 Hz cut-off frequency. b: input function is 2 Hz sinusoid with superimposed transient; output has been high pass filtered using 0.5 Hz cut-off frequency. Note the change in relative position of the transient.

phase shift with high pass filters, a wave was generated which had two components, a slow oscillatory wave (2 Hz) and a single fast transient as shown in the upper trace of Fig. 4b. Also shown in Fig. 4b is the output of the high pass filter, set at the 0.5 Hz cutoff. The low frequency component was, as expected, shifted to the left, i.e., made to lead the transient, while the high frequency transient was virtually stable. The extent of the shift was such that, in the unfiltered wave, the transient appears on the rising slope of the wave while, at the output of the filter, the transient appears on the falling slope. If these maxima were peaks in an evoked potential, the order of their appearance would actually be reversed by high pass filtering.

Experiment III

Method and Material

A click-evoked BAER was recorded from a Long-Evans rat, using the procedures of experiment I, except that the epoch was shortened to 6 msec and the output of the amplifier was sent to a Nicolet Pathfinder II, bypassing the Pathfinder's amplifier and filter system. Amplifier filter cutoffs were set at 0.1 Hz and 30 kHz. The resulting BAER wave form was then submitted to amplitude spectrum analysis using a software Fast Fourier Transform (FFT) program (Nicolet SPECTR). The stimulus artifact and the first 1 msec of the acoustic travel time were eliminated from the analysis. The epoch thus analyzed was 5 msec in duration, began 0.4 msec prior to arrival of sound at the ears, and ended just after the occurrence of N6. The result was regraphed on log-log paper to provide easy comparability with published spectra. Memory block size on all channels was 512 points.

Results

Fig. 5 displays the results of the analysis. Fig. 5b is the amplitude spectrum resulting from analysis of the final 5 msec of the wave form of Fig. 5a. The amplitude level rolls off from 200 c/sec (the resolution of the FFT analysis) down to about 5000 c/sec with small peaks in level at about 1000 and 2000 c/sec.

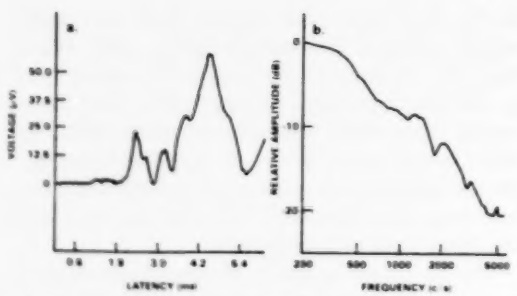

Fig. 5. Amplitude spectrum of BAER recorded from a Long-Evans hooded rat. a: BAER wave form. b: amplitude spectrum of a.

Discussion

These findings emphasize the potential for dramatic errors in scoring BAERs when analog filter settings are not chosen carefully. High pass filtering of rat BAERs at 400 Hz would seem to be responsible for the succession of 6 peaks appearing in some reports: the bifid P1 is altered to the extent that P1B is labeled P2, P2 is labeled P3, and so on down the line. It is also possible to shift the relative positions of predominantly high frequency and low frequency peaks due to the differential effects of high pass filtering, even when the cutoff is greatly removed from the lowest component frequency.

Experiment I quantified the shifts in peak latencies and amplitudes due to distortion which is also manifest in the shape of the overall wave form. In particular, two of the smaller peaks, P1B and P5, remained at their original latencies while the slower waves shifted forward in time. This phenomenon is consistent with the high pass filter effect illustrated in Fig. 4b, where the slow wave showed phase lead while the high frequency transient did not shift. Coincident with these differential latency effects, the peak-to-peak amplitudes of P1B and P5 grew as the other peaks were diminishing. The combined effect was to change the apparent identity of the peaks.

Compounding this difficulty is the potential, as shown in experiment II (Fig. 4b), for causing the peaks to exchange positions, an effect which occurred with high pass cutoff at 1/4 the frequency

of the slow wave. An analog filter with rapid rolloff produces considerable phase shift which extends well into the moderately attenuated portion of its frequency response curve. Less sharp analog filters have less extreme phase shifts, an effect which was manifest in the significant difference between low passing at 30 kHz using the less steep amplifier filter and filtering with the variable filter and the amplifier.

The rat BAER spectrum of experiment III is in fair agreement with the human BAER amplitude density spectra of Elberling (1979), Møller et al. (1981), Osterhammel (1981) and Hoke et al. (1984), and with the power density spectrum of Doyle and Hyde (1981). Analog filter cutoffs should be selected so that only small phase shifts occur at the highest and lowest component frequencies of significant amplitude. Given the high amplitude of the low frequencies found in the BAER wave form, regardless of its biological source, high pass filtering can be expected to produce phase, and therefore wave form, distortion. It is recommended that the lowest available cut-off frequency be used. The low pass cutoff should be selected to minimize effects on the high frequency components of the wave form. For example, a low pass cutoff of 20 kHz on the filter used here shifts the 2 kHz component of the rat BAER, which is 12 dB down, by 30°, and most of the rest of the spectrum by less than that.

Data presented here indicate that it is not sufficient to set cut-off frequencies just outside the limits of the wave form spectrum, because distortion due to phase shift can still occur when rolloff is steep. If cross-experiment generality and physiological interpretability are important, then a good maxim is to analog filter as little as possible. Even moderate analog filtering can differentially shift evoked potential components in time and, thereby, contribute to erroneous interpretations regarding the underlying physiology.

Résumé

Erreurs non reconnues résultant d'un filtrage analogique de la réponse auditive évoquée du tronc cérébral

Il a été montré que le filtrage analogique de la réponse auditive évoquée du tronc cérébral (BAER) et celui d'ondes synthétiques à l'aide de filtres à pente raide entraînent une distorsion significative, même lorsque les fréquences de coupure du filtre sont bien éloignées du spectre de l'onde. Le degré de distorsion est tel qu'il peut entraîner des erreurs d'identification des pics de la BAER. Des inversions dans l'ordre des pics peuvent survenir avec un passe haut réglé à seulement 1/4 de la fréquence composante la plus basse.

Les effets du filtrage ont été identifiés comme l'une des plus importantes sources de différences entre-laboratoires pour les BAER enregistrées chez le rat. Les fonctions de transfert des filtres pour un filtre analogique typique ont été établies pour le gain et la phase, en fonction de la fréquence. Le filtrage d'ondes artificielles a été utilisé pour révéler et mettre en évidence les effets de la distorsion. On a analysé spectralement chez le rat Long-Evans, une onde BAER typique et des conclusions ont été tirées à l'aide des bandes passantes appropriées.

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